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EXAMINER

EPPS, JANET L

ART UNIT PAPER NUMBER

1635

DATE MAILED: 06/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/753,169

Applicant(s)

STEIN ET AL.

Examiner

Janet L. Epps-Ford, Ph.D.

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 28 March 2003.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-47 is/are pending in the application.
- 4a) Of the above claim(s) 17-41 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-16 and 42-47 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

*Election/Restrictions*

1. Applicant's election with traverse of Group I, claims 1-16, and 42-47 in Paper No. 20 is acknowledged. The traversal is on the ground(s) that "if two or more independent and distinct inventions are claimed in one application, the Commissioner may require application to be restricted to one of the inventions," therefore Applicants argue that the sequence restriction should be withdrawn since the sequences are not independent. This is not found persuasive because contrary to Applicant's assertions the nucleotide sequences recited in the instant claims comprise a distinct nucleotide sequence and function to inhibit the expression of Bcl-xL protein expression in a distinct manner as per Applicant's Figure 6. Each of the various nucleotide sequences require an independent search of the prior art, wherein the search for one oligonucleotide sequence is not required for the other.
2. Moreover, Applicants argue that there is no serious burden on the Examiner to examine the sequences in the subject Application. In light of the fact that the instant claims have been amended to recite only SEQ ID NO: 4 and SEQ ID NO: 19 (having the same sequence as SEQ ID NO: 4), and since the examiner previously searched SEQ ID NO: 1-13 in copending application 09/832,648, and in parent application 09/109,614, the examiner withdraws the sequence restriction.
- JE* 3. It is noted that Applicants do not request that the restriction between groups I and II be withdrawn. However, the restriction between groups I and II is deemed proper for the reasons of record set forth in the Election/Restriction requirement mailed 2-24-03. Furthermore as per MPEP § 803, "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation of separate classification, or

separate status in the art, or a different field of search as defined in MPEP § 808.02." As set forth in the initial restriction requirement, group I is classifiable in 536/24.5 and group II is classifiable in 514/44.

The requirement is still deemed proper and is therefore made FINAL.

4. Claims 17-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 20.

#### ***Claim Objections***

5. Claim 4 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 4 recites "[T]he antisense oligonucleotide or claim 3, wherein the nucleotide sequence comprises nucleotide sequence SEQ ID NO:19." Claim 4 fails to further limit claim 3 because SEQ ID NO: 19 and SEQ ID NO: 4 comprise the same nucleotide sequence. Although the Sequence Listing indicates that SEQ ID NO: 19 comprises different modifications, nonetheless the nucleotide sequence of SEQ ID NO: 19 is the same as that of SEQ ID NO: 4.

#### ***Claim Rejections - 35 USC § 112***

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-2 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is drawn to an antisense oligonucleotide or analog thereof comprising 10 or more contiguous bases or base analogs from the sequence of bases of SEQ ID NO: 4. It is noted that the scope of this claim encompasses antisense oligonucleotides or analogs comprising 10 or more contiguous bases, or *antisense oligonucleotides or analogs comprising 10 or more base analogs from the sequence of SEQ ID NO: 4*. The instant claims are drawn to antisense oligonucleotides of undefined length comprising a minimal of 10 contiguous bases or base analogs from the sequence of SEQ ID NO: 4.

Claim 2 is drawn to an antisense oligonucleotide or analog thereof comprising a sequence having 90% or greater identity to SEQ ID NO: 4. The breadth of this claim encompasses sequences of undefined length comprising "a sequence" having 90% identity to SEQ ID NO: 4. The term "a sequence" recited in claim 2 is not specifically defined in either the claim or specification as filed, this term may therefore read on any number of nucleotide sequences, including wherein the antisense oligonucleotide of claim 2 may comprise a sequence of 5 nucleotides in length having 90% identity to SEQ ID NO: 4.

According to the specification as filed the antisense oligonucleotides of the present invention are disclosed as being functional to reduce or eliminate the expression of bcl-xL (see page 1, lines 19-20). However, the instant claims do not recite this particular functional limitation. The instant claims read on antisense oligonucleotide, i.e. one targeting any particular

gene from any particular organism, including all polymorphic and allelic variants of the claimed sequences.

One of ordinary skill in the art would not be able to predict the structures of all nucleotide sequences encompassed by the instant claims, because they comprise a broad number of nucleotide sequences, and there is no common structure shared among the species that is related to any particular common function, i.e. to reduce or eliminate the expression of bcl-xL, such that the ordinary skilled artisan would be able to immediately envision all nucleotide species encompassed by the instant claims, such that said nucleotide species are functional antisense oligonucleotides without the need for further experimentation.

See the January 5, 2001 (Vol. 66, No. 4, pages 1099-1111) Federal Register for the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement. These guidelines state: "[T]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention."

Applicants have not provided the nucleotide structures of the full scope of antisense oligonucleotides encompassed by the instant claims. It is evident that further experimentation would be required in order to identify the full scope of oligonucleotides encompassed by the claimed invention. Therefore, it is concluded that Applicants were not in possession of the full scope of the claimed antisense oligonucleotides at the time of filing of the instant application.

8. Claims 42-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the pharmaceutical compositions of the instant invention in an *in vitro* method, does not reasonably provide enablement for using the claimed pharmaceutical compositions *in vivo* for therapeutic purposes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to a pharmaceutical composition comprising an effective amount of the antisense oligonucleotide or analog thereof of claim 3 and a pharmaceutically acceptable carrier. The antisense oligonucleotide of claim 3 is an antisense oligonucleotide or analog thereof comprising nucleotide sequence SEQ ID NO: 4. The pharmaceutical compositions recited in the instant claims imply *in vivo* applicability for enablement purposes. The specification as filed teaches the use of the antisense oligonucleotide according to SEQ ID NO: 4 and a lipid delivery agent (a pharmaceutically acceptable carrier) for the treatment of cancer. However, the specification as filed does not provide sufficient guidance and/or instruction that would allow the skilled artisan to practice the full scope of the claimed invention without undue experimentation. This conclusion is based upon the following considerations. The

factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed Cir. 1988).

The quantity of experimentation required to practice the invention as claimed would require determining the modes of delivery in a patient *in vivo* such that the expression of the bcl-xL mRNA target is inhibited at a significant level and for a sufficient amount of time to produce the desired therapeutic effect, namely the broad treatment of any form of cancer, or specifically the treatment of prostate, epithelial, lung, or bladder cancer. Neither the specification as filed, nor the prior art searched, provides any specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

In regards to the amount of direction or guidance presented, the specification as filed does not provide sufficient guidance or instruction that would teach one of skill in the art how to successfully treat a human having cancer, broadly or specifically epithelial, prostate, lung or bladder cancer. The specification as filed provides only information regarding the ability of 4 chimeric PO/PS antisense oligonucleotides targeting bcl-xL to reduce the expression of bcl-xL in bladder and prostate cancer cells *in vitro* (see pages 34-36), by measuring the level of Bcl-xL protein expression using Western blot analysis. However, Applicant's own experiments (see Table 1) and specification suggest that the behavior of an antisense oligonucleotide in a cell may vary depending upon the cell-type, and delivery agent, see for example page 35, lines 12-17,

which states that identical oligonucleotides demonstrated different bcl-xL down regulation when delivered with different agents. Moreover, the examples do not provide any direct evidence of phenotypic effects on the antisense treated cells, for example there is no indication that cell growth was inhibited, see page 34, lines 19-22). Furthermore, the instant specification does not provided any clear nexus between inhibiting bcl-xL by antisense administration in bladder or prostate cancer cells *in vitro* and the treatment of cancer associated with bcl-xL expression in said cells. In addition, it is noted that the results obtained in the specification as filed was produced by using chimeric PO/PS oligonucleotides, the instant claims encompass unmodified oligonucleotides are not specifically limited to antisense oligonucleotides comprising this type of modification.

Regarding the level of predictability or unpredictability associated with the antisense therapeutic art, Crooke (1998), states "extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man [that] demonstrate that, even after careful consideration of all *in vitro* uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies [references omitted]." Furthermore, Crooke describes a variety of factors that influences the activity of antisense-based compounds. Crooke teaches that variations in cellular uptake and distribution of antisense oligonucleotides are influenced by a variety of factors: length of oligonucleotide, modifications, and sequence of oligonucleotide and cell type. The influence of non-antisense effects, for example phosphorothioate oligonucleotides tend to bind non-specifically to many proteins, wherein such protein binding influences cellular uptake, distribution, metabolism and excretion of said oligonucleotide. Additionally, non-

specific protein binding may produce effects that can be mistakenly interpreted as antisense activity, and may also inhibit antisense activity of some oligonucleotides. In addition to proteins, oligonucleotides may non-specifically interact with other biological molecules, such as lipids, or carbohydrates, wherein the chemical class of oligonucleotide will influence such interactions studied (Crooke, 1998; p. 3). Crooke clearly teaches that there is a significant level of factors, which influence the behavior of antisense based, compounds thereby rendering the activity of antisense compounds unpredictable.

Branch (1998) also teach that "Scientist seek to use the [antisense] molecules to ablate selected genes and thereby understand their functions and pharmaceutical developers are working to find nucleic acid based therapies. However, the antisense field has been turned on its head by the discovery of 'non-antisense' effects, which occur when a nucleic acid drug acts on some molecule other than its intended target-often through an entirely unexpected mechanism." In addition, Branch teaches that the successful delivery of antisense/ribozymes *in vivo* is unpredictable, the internal structures of the targeted RNA molecules and their association with cellular proteins can render target sites totally inaccessible *in vivo*. Moreover, Branch states that "[H]owever, their (*antisense molecules and ribozymes*) unpredictability confounds research applications of nucleic acid reagents."

Jen et al. (*Stem Cells*, Vol. 18: 307-319, 2000) provide a review of the challenges that remain before antisense-based therapy becomes routine in therapeutic settings. According to Jen et al. many advances have been made in the antisense art, but also indicate that more progress needs to be made. Moreover Jen et al. conclude that "[G]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has

remained elusive." It is also concluded that "[A] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." (see page 315, last two paragraphs).

It is apparent from Branch, Crooke, and Jen et al. that the art of antisense base therapeutics (at the time of filing) is unpredictable and those highly skilled in the art are working towards making the antisense therapy more predictable have many obstacles to overcome. Therefore, claims to antisense based pharmaceuticals and methods of treating diseases by the administration of said pharmaceuticals are subject to the question of enablement due to the high level of unpredictability in the antisense art.

Therefore, it is concluded that the amount of experimentation required for the skilled artisan to practice the full scope of the claimed invention would be undue based upon the known unpredictability regarding the delivery of antisense *in vivo* and further with the production of secondary effects such as treating a disease associated with the expression of a gene, and the lack of guidance in the specification as filed in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

#### ***Double Patenting***

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

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provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1-16 and 42-47 are provisionally rejected under the judicially created doctrine of double patenting over claims 9, 36-50, 53-54, 58, and 61-62 of copending Application No. 09/832,648 in view of Manoharan et al. Sanghvi et al., Matteucci et al. and Arnold et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending Application and the claims of the instant application are drawn to an antisense oligonucleotide or analog thereof comprising the nucleotide sequence according to SEQ ID NO: 4. The claims of the instant application specifically recite wherein the antisense oligonucleotide comprise the nucleotide sequence of SEQ ID NO: 4, however the claims in the copending application are drawn to antisense oligonucleotides comprising consecutive nucleotides, the nucleotide sequence of which is set forth in one of SEQ ID NOS; 1 and 3-13, wherein one or more sugar of the oligonucleotide contain an -OMe group at its 2' position. The claims of the copending application encompass antisense oligonucleotides comprising the nucleotide sequence of SEQ ID NO: 4. The claims of the instant application are drawn to antisense oligonucleotides or analog thereof, the specification as filed describe analogs of the antisense oligonucleotides of the present invention which encompass 2'-OMe modified oligonucleotides, see page 10, lines 3-8. The term "analog thereof" encompasses the 2'-OMe group recited in the claims of the copending application. Therefore, the antisense oligonucleotide or analog thereof comprising SEQ ID NO: 4 as recited in the instant claims and the antisense oligonucleotides comprising the nucleotide sequence of SEQ ID NO: 1 and 3-13 as

recited in the claims of the copending application overlap in scope. Moreover, the genus of compounds encompassed by the copending claims is so small that each species of nucleotide sequence according to SEQ ID NO: 1 and 3-13 that the nucleotide sequence species according to SEQ ID NO: 4 is instantly envisioned.

However, the claims of copending application 09/832,648 do not recite wherein the oligonucleotide is conjugated to a peptide, cholesteryl moiety, or a liposome, wherein the phosphorothioate modification is stereoregular, wherein the oligonucleotide comprises one or more short chain alkyl structures, or a C-5 propynyl modification.

Manoharan et al. teach the design and use of derivatized antisense oligonucleotides, wherein derivatization of said antisense oligonucleotides results in improved transfer across cellular membranes (page 5, lines 7-9). The compounds of Manoharan et al. comprise a plurality of linked nucleosides wherein at least one of the nucleosides is functionalized at the 2'-position with a substituent such as for example, a peptide, a protein, a steroid molecule, a lipid soluble vitamin, a lipophilic molecule and a porphyrin (page 5, lines 20-30).

Sanghvi et al. disclose oligonucleotide analogs comprising short alkyl stretches in place of the phosphodiester backbone. These oligonucleotide analogs are disclosed as having improved nuclease resistance and improved cellular uptake in comparison to unmodified oligonucleotides, see col. 1, lines 58-65, and formula I, col. 4.

Matteucci et al. disclose oligonucleotides comprising C-5 propyne modified nucleobases, oligonucleotides comprising these modifications have enhanced RNA binding affinity (see Table II, col. 20).

Arnold et al. teach that oligonucleotides comprising chirally pure internucleoside linkages, wherein the internucleoside linkage may include phosphorothioate, have enhanced binding affinity for their target and enhanced nuclease resistance. See for example, col. 3, lines 30-67, and col. 5, lines 19-29.

It would have been obvious to one of ordinary skill in the art, at the time of filing, to modify the antisense oligonucleotides recited in co-pending application 09/832,648 with the teachings of Manoharan et al., Sanghvi et al. Matteucci et al., and Arnold et al. in the design of modified antisense oligonucleotides as recited in instant claims 5-16. One of ordinary skill in the art would have been motivated to modify antisense oligonucleotides as taught by Manoharan et al. Sanghvi et al., Matteucci et al. and Arnold et al. because these modifications are disclosed as being useful to confer enhanced properties to oligonucleotides comprising the modifications taught in their respective teachings. Some of these enhanced properties include, for example, increased nuclease resistance, enhanced cellular uptake, and enhanced stability of hybrids formed between the target nucleic acid and the oligonucleotide.

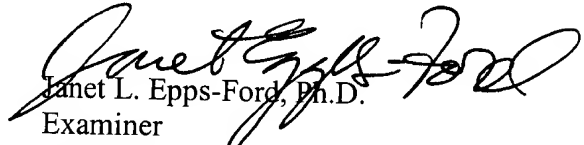
Therefore, the claims of the instant application are an obvious variation of the claims in the copending application. Moreover, if US Patents were granted to the claims of the instant application and to those of the co-pending application the resultant double patenting of common subject matter may result in possible harassment by multiple assignees.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on M-T, Thurs-Fri, 8:30AM-6:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-746-5143 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

  
Janet L. Epps-Ford, Ph.D.  
Examiner  
Art Unit 1635

*JLE*  
June 16, 2003